REMARKS

The Examiner's Action mailed November 22, 1995, has been received and its contents carefully noted.

The specification has been amended to insert section titles therein in accordance with U.S. Patent practice, a new abstract has been added and the abstract has been reproduced on a separate sheet which has been attached to this Amendment.

Support for the amendment to claims 16, 21 and 22 can be found, for instance at page 5, lines 5 to 18 and in the results of page 17.

Claims 15-22 are now active in the application and are believed to be in allowable condition.

I. Relying of 35 U.S.C. § 102(b), claim 15 stands rejected as being anticipated by Wilson et al. (WO 87/04462). Applicants respectfully request reconsideration of this rejection.

Submitted with this Response is a new Declaration signed by inventors Bebbington, Yarranton and Wilson. Please note that this application now claims priority to application Serial No. 08/302,241 filed September 8, 1994, which is a continuation of application Serial No. 08/165,533 filed December 13, 1993, now abandoned, which is a continuation of

application Serial No. 07/852,390 filed March 16, 1992, now abandoned, which is a continuation of application Serial No. 07/595,733 filed October 10, 1990, allowed as U.S. Patent 5,122,464, which is a continuation of application Serial No. 07/117,071 filed October 23, 1987. Application Serial No. 07/117,071 was filed under 35 U.S.C. 371 as the U.S. national stage application of PCT GB/87/00039 which claims priority to application GB 8601597, filed January 23, 1986.

Applicants respectfully submit that the priority date for the instant application is now January 23, 1986. As the WO 87/04462 publication (which is identical to PCT GB/87/00039) was published on July 30, 1987, Wilson et al. cannot be considered prior art against the instant application. Accordingly, Applicants respectfully request the withdrawal of the rejection of claim 15.

II. Relying on 35 U.S.C. §103, claims 16-22 stand rejected as being unpatentable over Wilson as applied to claim 15 above and further in view of Ringold (USPN 4,656,134) and Foecking. Applicants respectfully request reconsideration of this rejection.

Applicants' vectors according to the claims are submitted to be neither disclosed in nor suggested by any reasonable combination of the teachings of the applied references for the reasons which follow.

The Examiner asserts that the vectors of Wilson et al. differ from the claimed invention in that they do not comprise promoters of different strength. To cure this deficiency, the Examiner relied on the teachings of Ringold and Foecking. The Examiner asserts that Ringold teaches using promoters of different strength with multiple genes linked in tandem arrangement, that the genes may be transcribed in the same direction and that the selectable gene is upstream of the heterologous gene of interest.

Applicants respectfully submit that the use of different strength promoters is but one of the differences in the claimed invention. In addition to promoter strength, Applicants unexpectedly found the order of the genes and direction of transcription for each of the heterologous genes in relation to the GS gene was of the utmost importance. Applicants respectfully submit that the statements of Ringold as to the order and direction of transcription are at best ambiguous and do not address the unexpected advantages to the gene order and direction of transcription of the vectors in claims 16 to 22.

For instance, Ringold et al. state that:

> "while the amplifiable gene and the gene of interest **may be transcribed in the same or different directions** or have the coding (sense) strand on the same or different strands, usually they will be transcribed in the same direction and from the same strand" (column 3, lines 29-34).

In contrast to the statements of Ringold that the gene order and direction of transcription may be in either order, the results of the instant specification teach that the gene order and direction of transcription in the claimed vectors must be arranged to prevent transcriptional interference. For instance, the specification teaches:

> "It has been observed that other vector arrangements, for instance using different promoters or different ordering or orientation of the genes, can lead to a much reduced or even non-existent level of GS or heterologous protein production. It is conjectured (although applicants do not which to be limited to this theory) that if a gene containing a strong promoter is located upstream of a GS gene having a weaker promoter, the transcription of the upstream gene will run through into the downstream gene, thus producing occlusion of the downstream promoter" (page 5, lines 5-14).

As a specific example, Applicants unexpectedly found that placing the GS gene downstream of the heterologous cLc gene (pcLc2GS) yields a vector that upon transfection does not yield glutamine-independent colonies (see page 17, lines 13-18). This is in contrast to vector pSV2GS.cLc which has the gene order reversed, e.g. the GS gene upstream of the heterologous cLc gene so that transcription of the cLc gene does not proceed through the GS gene. Upon transfection, pSV2GScLc yields glutamine-independent colonies comparable to the vector which encodes GS alone (see page 17, lines 15-18).

No where in the entire Ringold patent is there a mention that transcriptional interference or promoter occlusion may be a problem to be considered when designing the gene order and direction of transcription of the selectable (amplifiable) and heterologous gene(s) of interest. In fact, Ringold expressly states that "the amplifiable gene and the gene of interest **may be transcribed in the same or different directions**" (column 3, lines 29-31). Thus, Ringold states that vectors may be prepared that allow transcription of the heterologous gene through the amplifiable or selectable gene. This was found not to be the case when vectors comprising the GS gene are used to transform cells to glutamine-independence.

Applicants respectfully submit that claims 16 to 22 each recite limitations ensuring that the expression of the heterologous gene(s) does not interfere with the promoter for GS. These limitations ensure that transcription from the heterologous gene(s) do(es) not proceed through the GS gene and promoter.

As to the Examiner's assertion that Ringold et al. teach that the amplifiable or selectable gene is upstream of the heterologous gene(s) of interest, Applicants respectfully submit that the order of the genes set forth at column 3, lines 7-22 is nothing more than a **description** of the gene order of the vectors made by Ringold. Ringold does not

provide a reason for this gene order, does not state that the order is a requirement and does not recognize promoter occlusion problems with the GS gene. Furthermore, Ringold states in the same column that the genes may be oriented in either direction. Accordingly, the statements of Ringold do not provide the needed instructions as to the required gene order and direction of transcription set forth in the pending claims. These limitations in the pending claims are those which Applicants unexpectedly found were required to enable production of glutamine-independent cell lines with the claimed vectors.

Applicants respectfully submit that unobviousness can reside in the discovery of the source of a problem. In re Sponnoble, 160 USPQ 237, 243 (CCPA 1969). A copy of Sponnoble is attached for the Examiner's convenience. In Sponnoble, the inventor discovered that the primary cause of moisture transmission between separate dry and aqueous compartments in a pharmaceutical vial was through the permeability of a rubber plug rather than leakage between the plug and the vial wall. Id.

In the instant application, Applicants have discovered that placing the heterologous gene with a strong promoter upstream of the GS gene prevents that ability to produce glutamine-independent cells with the vector. Applicants have also discovered the solution to this problem which entails

constructing the vectors so that transcription of the heterologous gene(s) does not proceed through the GS gene.

Just as in Sponnoble, where the Court of Customs and Patent Appeals found that the discovery of the source and solution to a problem of moisture transmission between the dry and aqueous compartments of a pharmaceutical vial should be considered in determining the unobviousness of the invention, the discovery and solution of the inability to obtain glutamine-independent cell lines caused by transcription run through from the heterologous gene into the GS gene should be considered when evaluating unobviousness of the claimed vectors. Given this precedent, Applicants respectfully submit that the claimed vectors cannot be found to be obvious over Wilson et al. in view of Ringold (USPN 4,656,134) and Foecking. This is especially the case when none of the cited references recognizes the potential problem and when Ringold suggests that the genes may be aligned in either direction.

CONCLUSIONS

In view of the foregoing amendments and remarks, it is requested that the rejections of record be reconsidered and withdrawn, and that the Application be found to be in allowable condition.

If the Examiner believes that a conference would be of value in expediting the prosecution of the Application, she is invited to telephone undersigned Counsel.

Respectfully submitted,

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